Exhibit B

EXPERT REPORT OF CHRISTINA PRAMUDJI, M.D.

The following is a summary of my qualifications and my opinions in this case as of the date of this report. This report is based on the information I have now. To the extent I receive additional information between now and the time of the trial, I may form additional opinions or some of my opinions may be modified.

All of my opinions are held to a reasonable degree of medical and scientific certainty and probability. Below is a summary of my general opinions as set forth in more detail in my report. All of my opinions are based on my education, training, and clinical experience, the medical literature and materials that I have reviewed, my discussions with colleagues, my research and review of the medical records and deposition testimony provided to me in this case, and from the perspective of a board-certified urologist with subspecialty board certification in Pelvic Floor Medicine and Reconstructive Surgery.

- Urinary incontinence, including stress and urge incontinence, are common conditions in women. There are many risk factors for incontinence, and more specifically stress urinary incontinence.
- Incontinence can be very distressing and burdensome to women and can cause adverse effects on women physically, mentally, and socially. Incontinence can adversely affect quality of life and relationships.
- Stress urinary incontinence can be treated with lifestyle changes and behavioral therapy, non-surgical options and surgery. More conservative

efforts to treat incontinence may not be a suitable option for some women and they may not always provide relief. Many women who try more conservative measures will discontinue the therapy.

- Surgery for stress urinary incontinence has been shown to be the most definitive treatment. Surgeries include the Burch colposuspension, native/biologic tissue slings and most often, synthetic slings made of monofilament, large pore polypropylene like that used in TVT and TVT-O. The clinical data shows that the TVT and TVT-O Type 1 macroporous Prolene polypropylene mesh is biocompatible, has a minimal inflammatory response, allows for adequate tissue ingrowth and is not associated with a significantly increased risk of infection over that generally associated with SUI and vaginal surgery, which is consistent with my clinical experience in hundreds of women. The data in women does not support that the TVT and TVT-O mesh is cytotoxic, causes an adverse inflammatory response, sarcoma or cancer, or that the way the edges are cut has any clinically significant effect. The data in women also does not support that the TVT and TVT-O mesh degrades, or that if it did it would have a clinically significant effect, and I have not seen evidence of mesh degradation in my clinical practice.
- The TVT and TVT-O have a positive benefit to risk profile. Overall, the TVT and TVT-O have a better benefit/risk profile than the Burch and native tissue slings. The TVT and TVT-O have great utility to surgeons and their patients. Extensive data exist which supports the TVT and TVT-O and shows that they

are minimally invasive and less invasive than the Burch and native tissue slings. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, faster recovery, and reduced complications, including voiding dysfunction. Polypropylene mesh has been used for decades. TVT and TVT-O are safe and effective surgical options for the treatment of SUI.

- The TVT and TVT-O slings have been extensively studied. The TVT and TVT-O slings have been studied in over 100 Randomized Controlled Trials (RCTs) and hundreds of other studies. The TVT and TVT-O have also been extensively used in clinical practice by urologists, gynecologists, and urogynecologists. The TVT and TVT-O are taught to doctors during residency and fellowship because they are recognized as a suitable surgical options to treat stress urinary incontinence.
- The TVT and the TVT-O are the Gold Standard and standard of care for treating stress urinary incontinence. Overall cure and improvement rates are generally in the 80-95% range with significant improvements in symptoms and quality of life. Complications are infrequent and manageable. The rate of mesh exposure is 1-2%, voiding dysfunction and retention is about 1-4%, and complications requiring surgical management occur at a rate of 2-4%. Dyspareunia and pain are also rare (<1%) and occur more often with the Burch and native tissue slings. Thus the risk of surgery due to mesh exposure or erosion, voiding dysfunction and retention, and pain is rare even out to

10-17 years follow up according to high level data. The need for a second revision is very uncommon according to the reliable scientific data. Case reports and case series are of limited value and do not address the incidence of complications or primary and secondary management.

- The TVT and TVT-O have been studied and evaluated by members of the pertinent medical and surgical organizations, such as the American Urologic Association (AUA), Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU), American Urogynecologic Society (AUGS), International Continence Society (ICS), National Institute for Health and Care Excellence (NICE), Society of Gynecologic Surgeons (SGS), International Urogynecological Association (IUGA), and the European Association of Urology (EAU), and are found to be safe and effective and widely recognized as the Gold Standard, standard of care, and first line and suitable surgical option to treat stress urinary incontinence.
- All surgeries to treat stress urinary incontinence have risks. Like the TVT and TVT-O, other SUI surgeries are performed in the pelvis and utilize surgical instruments, like Stamey needles, in the surgical field. Potential risks of operating in this area are well described to surgeons during training, in medical textbooks, and in the medical literature, and are well known risks. The same is true for the tensioning of sutures as well as slings, whether made of synthetic or animal or native tissue, and the potential complications such as voiding dysfunction. Pain, pelvic pain, and dyspareunia can occur with any

SUI surgery and vaginal surgery, are well known and described in the literature, as well as taught to surgeons in their education and training. Dyspareunia and sexual dysfunction that preexists in women can also be cured or improve following TVT or TVT-O placement. Mesh exposure/erosion is the only unique risk when using the TVT and TVT-O and it is uncommon and can be easily treated in the majority of cases. Suture and sling erosion and wound complications can occur with non-TVT/TVT-O SUI surgeries. The TVT and TVT-O are not defective in their design and from my perspective as a surgeon, the risks are adequately described in the IFU and professional education materials.

- Although some of Plaintiffs' experts claims that another material, such as PVDF, Prolene Soft, Vypro or Ultrapro that has been used in hernia and prolapse repair, should be used, they point to no similar breadth and length of clinical data in SUI patients to make such comparisons. Nor have they provided data showing that these meshes would work long term in the design of the TVT or TVT-O, which have long term data. These meshes have not been studied to treat SUI in women like TVT and TVT-O. These claims are without adequate scientific support and merit.

I. BACKGROUND, TRAINING AND EXPERIENCE

I am a board certified urologist, with a subspecialty board certification of Pelvic Floor Medicine and Reconstructive Surgery. I received a Bachelor of Science in Chemical Engineering from Georgia Institute of Technology (Georgia Tech) *cum laude*, which included a Chemical Engineering Internship at the University of London. I received my M.D. degree from the University of Alabama School of Medicine in Birmingham in 1996. I then completed a general surgery and urology residency at Baylor College of Medicine in Houston, Texas, where I received extensive training in pelvic floor medicine and surgery. During this training I performed various surgeries to treat urinary incontinence and other pelvic and urologic conditions and disorders. Since then I have been in private practice for over 12 years and the focus of my practice is female urology and pelvic floor medicine.

I have a vast experience with mid-urethral slings, having performed over 900 sling procedures from various manufacturers and of various approaches. I am very familiar with the Ethicon TVT and TVT-O devices, having been trained in their use and having surgically placed them in hundreds of procedures. I have been a consultant for Ethicon and Boston Scientific in sling development. I also have extensive mesh experience in over 600 cases and have managed mesh complications, as well. I have an interest in bladder and pelvic floor surgery, so when I realized that the majority of my practice involved women with those sorts of problems, I decided to make it the major focus of my practice. A copy of my curriculum vitae, which details my training,

education and experience, is attached as **Exhibit "A"** to this report. A list of my publications is also set forth in my CV.

II. CHARGES AND TESTIMONIAL HISTORY

For my work in this case, I am charging $600 an hour for time spent reviewing and preparing. I charge $700 an hour for deposition or court testimony. In the past four years, I have given testimony as an expert in the following: Connie & Kevin Schubert v. Freeman Health System et al., Jasper County Missouri Case No. 10AO-CC00219 (8/27/2013 deposition testimony), Carolyn Lewis v. Johnson & Johnson, et al., Case No.: 2:12-cv-04301 (1/10/2014 deposition testimony), and Huskey/Edwards v. Johnson & Johnson, et al., (4/11/2014 deposition testimony and 9/3-4/2014 trial testimony).

III. MATERIALS REVIEWED

In this case, I have reviewed the medical records and the available deposition transcripts. I have reviewed the expert reports submitted by the plaintiffs, specifically the reports of Drs. Rosenzweig, Margolis and Carey, as well as the materials cited in the reports and their expert depositions.

I have also reviewed the IFU for Ethicon's TVT-O product, the Patient Brochure, as well as the professional education materials used by Ethicon relating to the TVT and TVT-O procedures. Through my training, clinical and surgical experience, professional activities including CME and conference attendance, my lecturing and professional education to other pelvic floor surgeons, and my review of the literature, I am familiar with urinary incontinence, the treatment of incontinence, the TVT and TVT-O, and the

medical literature relating to the development of TVT and TVT-O and their safety and effectiveness. In preparation for my testimony, I have reviewed some of that literature, as set out in **Exhibit "B**." Exhibits that will be used to support my findings and opinions, as well as documents that I have reviewed, are identified above, cited in my report, and listed in **Exhibit "B**" as well. These materials and the examination, in addition to my personal experience, knowledge, training, and education, have informed the opinions referenced above and which follow.

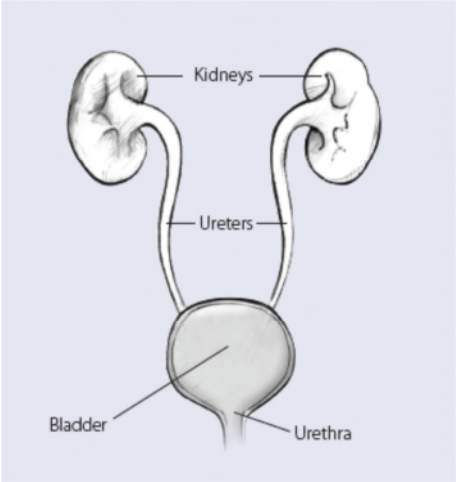
IV. OPINIONS

My conclusions and opinions are based in the practice of evidence-based medicine. As state above, I hold all opinions set forth in this report to a reasonable degree of medical and scientific certainty and probability.

A. Urinary Incontinence

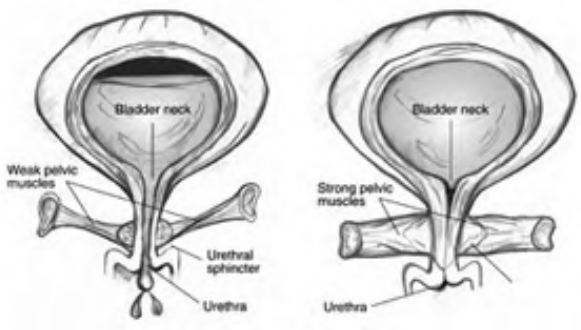
Urinary incontinence is the involuntary leakage of urine and is a common condition in women. Incontinence can be a result of different abnormalities of function of the lower urinary tract or as a result of other illnesses, which tend to cause leakage in different situations. There are different types of incontinence including stress urinary incontinence (SUI), which occurs with exertion, coughing, sneezing, or other activity or movement, and urgency incontinence, which is the involuntary leakage of urine that follows a sudden need to urinate and is caused by the bladder muscles contracting. Women can have either or both of these types of incontinence and when both are present it is termed mixed incontinence.

As can be seen in the diagram, the bladder is the organ in our body that holds urine. Waste is filtered by the kidneys and urine flows down the ureters connecting the bladder. Connected to the bladder is a tube called the urethra. The urethra is at the bottom of the urinary tract and allows urine to be passed from the body.



(AUA Foundation 2013 A Patient's Guide, 1 in 3 Women experience Stress Urinary Incontinence.)

Involuntary leakage of urine with SUI results when intra-abdominal pressure increases and exceeds the ability of the urethra to stay closed.



There are many factors associated with the development of SUI. Risk factors include increasing age, obesity, parity and vaginal delivery, diabetes, hormone replacement therapy, and family history. Other factors, including hysterectomy, physical activity and smoking have been reported to increase the risk of SUI. Caucasian and Hispanics have an increased risk of SUI. Nerve injuries to the lower back and pelvic surgery are also potential risk factors for development of SUI because they weaken the

pelvic floor muscles. (Stress Urinary Incontinence, A Monograph from the AUA Foundation 2011).

Although prevalence of incontinence varies by study cohort and definition, it is common. For example, SUI has been reported to occur in up to 35% of women. A study of the National Health and Nutrition Examination Survey (NHANES) in 4,229 women aged 20 or older showed that 49.6% reported urinary incontinence symptoms, and of those 49.8% reported pure stress incontinence, 34.3% mixed incontinence and 15.9% pure urge incontinence. (Dooley Y, et al. Urinary incontinence prevalence: results from the National Health and Nutrition Examination Survey. J Urol. 2008; 179:656-61.)

Comparative data from NHANES 2007-2008 show an increase in the prevalence of UI in women to 53.4%, which was partially explained by differences in age, race/ethnicity, obesity, diabetes and select chronic diseases. (Markland AD, et al. Prevalence and trends of urinary incontinence in adults in the United States, 2001 to 2008. J Urol. 2011; 186:589-93).

In another NHANES survey of nonpregnant women, the prevalence of SUI increased as women got older. There the authors focused on moderate or severe urinary incontinence (a score of > or =3 on a validated incontinence severity index -- at least weekly or monthly leakage of more than just drops) and posited that it reflected the population of women more likely to seek treatment. Moderate to severe SUI was reported to affect 6.9% of women 20 to 39 years old, 17.2% in 40 to 59 years old, 23.3% in those 60 to 79 years old, and 31.7% in women 80 years or older. (Nygaard I, et al.

Pelvic Floor Disorders Network. Prevalence of symptomatic pelvic floor disorders in US women. JAMA. 2008; 300:1311-6.) The prevalence was also found to increase with childbirth and for women who were overweight or obese.

In a study of women presenting with noncancerous gynecologic conditions, just over half had symptoms of coexisting urinary incontinence, and on average, an additional 4% developed UI each year. (Wu JM, et al. Prevalence and incidence of urinary incontinence in a diverse population of women with noncancerous gynecologic conditions. Female Pelvic Med Reconstr Surg. 2010; 16:284-289.) Many women reported symptoms of urinary urgency, nocturia and incomplete bladder emptying. Additionally, it was noted that less than half of women with incontinence advise their healthcare providers of their symptoms. This often may be because of the embarrassment and stigma associated with incontinence. (Stress Urinary Incontinence, A Monograph from the AUA Foundation 2011).

Urinary incontinence can adversely affect the well-being of women and cause distress and embarrassment, with lifestyles, relationships and careers being profoundly implicated. SUI can lead women to isolate themselves, to limit their work and social life, and curtail activities such as trips, exercise and attending family and other social gatherings. Studies have shown that SUI imparts adverse psychosocial impacts, social embarrassment and avoidance and limiting behaviors, including depression and anxiety about having sex and engaging in numerous other activities. (Fultz NH, et al. Burden of stress urinary incontinence for community-dwelling women. Am J Obstet Gynecol. 2003;

189:1275-82). Urinary incontinence can lead to urinary tract infections, cellulitis, pressure ulcers, sleep deprivation, social withdrawal, depression, and sexual dysfunction.

The diagnosis of SUI is based on involuntary urine loss from the urethra coincident with increased abdominal pressure (positive stress test) such as that occurring during coughing and straining in a patient who complains of stress incontinence. (Dmochowski RR, et al. Update of AUA guideline on the surgical management of female stress urinary incontinence. J Urol. 2010; 183:1906-14 (2010 AUA SUI Guidelines)). Urodynamics may also be used to diagnose or confirm SUI.

B. Non-Surgical Treatment of SUI

SUI may be treated in different ways, including lifestyle changes/behavioral therapy, non-surgical treatment and surgical treatment. Lifestyle and behavioral therapies include bladder training, scheduled toilet trips, fluid and diet management, weight loss, smoking cessation, and modification of medications in the case of side effects. These therapies can be combined with others. There are no FDA-approved medications for the treatment of SUI.

Nonsurgical options include behavior muscle therapy (Kegel exercises) and the use of a pessary, which is a device inserted into the vagina to support the pelvic area and urethra to relieve mild symptoms. Kegel exercises have shown to improve mild to moderate urge and stress incontinence. Approximately 65% will experience some improvement, but only 15-28% of women have a 100% cure rate (no incontinence

episodes) and after 3-15 years, 25-50% will have undergone surgery. (Labrie J, et al. Protocol for Physiotherapy Or TVT Randomised Efficacy Trial (PORTRET): a multicentre randomized controlled trial to assess the cost-effectiveness of the tension free vaginal tape versus pelvic floor muscle training in women with symptomatic moderate to severe stress urinary incontinence. BMC Womens Health. 2009; 9:24, citing Alewijnse D, et al. Effectiveness of pelvic floor muscle exercise therapy supplemented with a health education program to promote longterm adherence among women with urinary incontinence. Neurourol Urodyn 2003; 22:284-295; Goode PS, et al. Effect of behavioral training with or without pelvic floor electrical stimulation on stress incontinence in women: a randomized controlled trial. JAMA 2003; 290:345-352; Cammu H, et al. Who will benefit from pelvic floor muscle training for stress urinary incontinence? Am J Obstet Gynecol 2004; 191:1152-1157; Bo K, et al. Lower urinary tract symptoms and pelvic floor muscle exercise adherence after 15 years. Obstet Gynecol 2005; 105:999-1005; Lamers BH & Vaart CH van der. Medium-term efficacy of pelvic floor muscle training for female urinary incontinence in daily practice. Int Urogynecol J Pelvic Floor Dysfunct 2007; 18:301-307.)

Pessaries must be removed for cleaning or sexual activity and can lead to vaginal discharge, odor, pain, bleeding and erosion. Like pelvic floor exercises, many women discontinue pessary use. In a one year randomized trial, only 45% of women reported that they were still using the pessary at one year and only 57% of women reported that they were continuing to practice their pelvic floor muscle exercises. (Richter HE, A Trial

of Continence Pessary vs. Behavioral Therapy vs. Combined Therapy for Stress Incontinence (ATLAS); Obstet Gynecol. 2010; 115:609–617.)

C. Bulking Agents

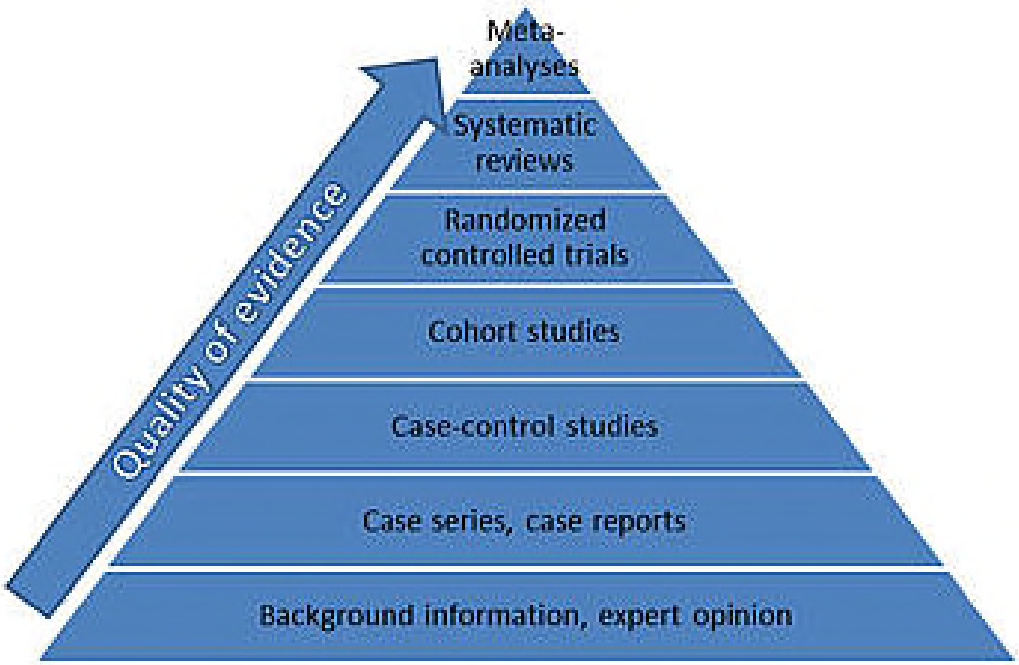
Injectable agents (bulking agents), like collagen, are sometimes used to treat SUI. The agent is injected into tissues around the upper portion of the urethra. This is usually performed under anesthesia, frequently local, via a cystoscope which is passed through the urethra. These agents work by bulking the area around the urethra. Injectable agents are not a permanent repair and efficacy is lower than that achieved with surgery. Fewer than 4 out of 10 women have long-term benefits. The cured/dry estimates for patients treated with collagen decrease from 48% at 12-23 months to 32% at 24-47 months. (AUA SUI Guidelines 2010). Many women will need multiple injections to maintain continence, and the main risks are pain at the injection site, injury to the urethra, and migration of the bulking material.

D. Surgical Treatment of SUI -- TVT / TVT-O

Surgery for SUI has been shown to be the most definitive treatment. Surgery for SUI includes the Burch colposuspension, native/biologic tissue slings and most often, synthetic slings. Monofilament, large pore polypropylene like that used in TVT and TVT-O, is the most common type of synthetic material used in slings.

The TVT and TVT-O slings have been studied extensively, in over 100 randomized controlled trials (RCTs) and many more other studies, systematic reviews, Cochrane

Reviews, metaanalyses, professional society guidelines, analyses, reviews, and position statements. These data are of the highest level of medical and scientific evidence pursuant to the Oxford Levels of Evidence as shown below in the levels of evidence pyramid:

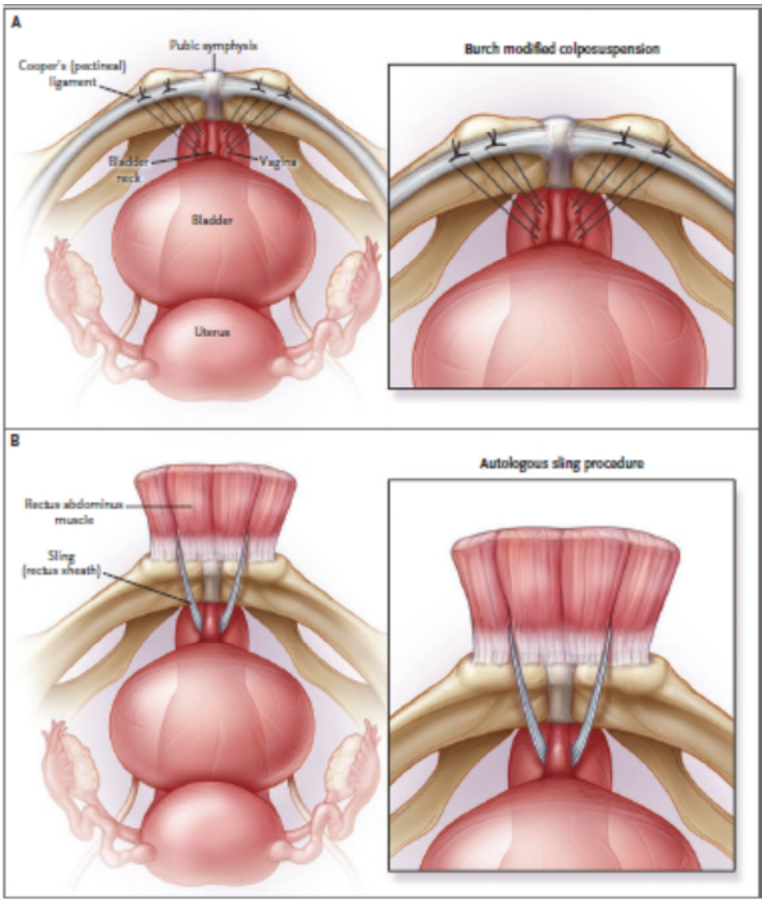


(http://www.cebi.ox.ac.uk/for-practitioners/what-is-good-evidence.html)

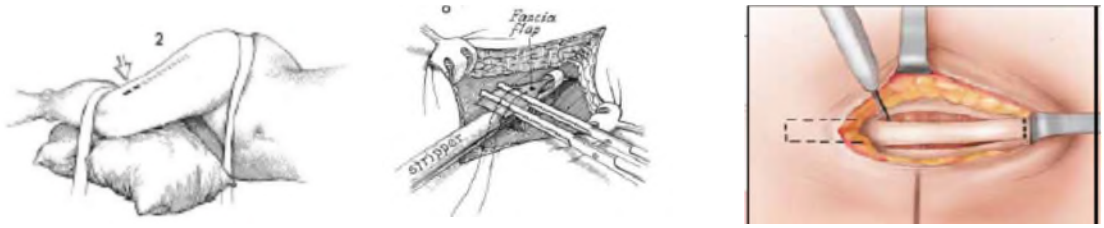
My opinions are based on these high level data and thus my opinions are evidence based, unlike to Plaintiffs' experts who rely on materials which are of the lowest level evidence such as case reports and case series, and in many cases simply irrelevant such as emails, documents, literature and excerpts of testimony concerning hernia mesh and prolapse devices.

The data on the TVT and TVT-O surpasses that of other procedures like the Burch colposuspension and the autologous pubovaginal sling, as well as all other slings. Of all the sling procedures, the Type 1 macroporous, monofilament, polypropylene mesh used in the TVT and TVT-O has the longest and broadest track record of safe and effective use. Other types of surgeries to treat SUI in the past, such as Marshall-Marchetti-Krantz (MMK) procedure, anterior colporrhaphy and needle suspension procedures, have declined and are not now recommended by the pertinent medical associations.

The Burch colposuspension procedure can be performed open or laparoscopically under general anesthesia. Access to the bladder and urethra is achieved by making an incision in the abdominal wall. In the Burch, the vaginal wall is attached to the Cooper's ligament next to the pubic bone. Cystoscopy may also be performed during the Burch. Patients are required to stay in the hospital longer than for a TVT procedure, which can be performed with local or regional anesthetic. Surgery and recovery times are longer with the Burch compared to the TVT. Although the laparoscopic approach to the Burch is available to some physicians, disadvantages include the difficulty in teaching the technique, a steep learning curve for laparoscopic suturing, the requirement for general anesthesia, abdominal entry, pneumoperitoneum, and three or four abdominal incisions.



The pubovaginal sling procedure is usually performed using general anesthesia. This sling requires an abdominal incision to harvest a rectus fascia graft or leg incisions to harvest a fascia lata graft. This can be done with a scalpel, electrocautery or with the aid of a tissue stripper.



Cadaveric slings are not commonly used because of decreased efficacy and lack of durability (resorption and integration risks) and issues with rejection and questions of durability of xenogenic (mostly porcine) tissue slings also limits their use. After a vaginal incision is made, Stamey needles or long clamps are passed from the abdominal incision through the retropubic space. After cystoscopy, the harvested strip of fascia is pulled up transvaginally and the sling is tensioned with a surgical instrument similar to that with a TVT and attached to the rectus fascia with permanent sutures.

While some of plaintiffs' experts claim that another material such as PVDF, Vypro or Ultrapro should be used, they point to no similar breadth and length of clinical data in SUI patients to make such comparisons nor have they provided data showing that these meshes would work long term in the design of the TVT or TVT-O which have long term data. The reason is simple – they cannot. These meshes have not been studied to treat SUI in women like TVT and TVT-O. Their methodology is severely compromised and in effect, unscientific. I know of no pelvic floor surgeons in the state of Texas or in the United States who use PVDF or kits employing PVDF to treat SUI or mixed UI. The same can be said for Vypro and Ultrapro mesh.

Urology, gynecology and urogynecology specialists and surgeons like me turn to the TVT and TVT-O because it is proven and it works. It is endorsed by urology, gynecology and urogynecology professional societies in the United States, Europe and internationally whereas Plaintiffs' experts' posited alternative mesh design for SUI are not. Also while Vypro, Gynemesh PS and Ultrapro mesh have been suggested as

potential better design, I would have concern with a potential decrease of efficacy if utilized as a sling given the mesh in a SUI sling is only about 1 centimeter wide. This narrow strip of tape needs pores like that in the TVT and TVT-O mesh as the mesh provides for a backboard at the midurethra. Vypro and Ultrapro also have a partially absorbable component and the data do not show that these meshes would work in the TVT design as the mesh sticks to the sheath and tears apart upon sheath removal, losing integrity. Moreover, when used in pelvic organ prolapse repair they have not been demonstrated to be more efficacious or safer and have exposure rates of 15% and dyspareunia. (Jacquetin 2004 ICS; Milani 2012)

The pore size for the TVT and TVT-O mesh is macroporous (> 75 microns) and allows the cells needed to address bacteria and promote tissue incorporation. Plaintiffs' experts' claim that 1,000 microns are needed in each direction in order for a mesh to have effective porosity is a theory and artificial construct and the clinical data on the TVT and TVT-O mesh as discussed later is inconsistent with this theory. Moreover, the porosity of the TVT and TVT-O mesh is among the largest for any SUI sling and is optimal for use in the TVT configuration. Lastly, these other meshes can also lead to mesh exposure, which is a wound complication.

There are risks with all surgeries. All SUI surgeries have potential risks. All surgical procedures to treat SUI can fail. All surgical procedures have some degree of pain and discomfort. All surgical procedures to treat SUI may require reoperation for failure or to treat complications. For example, as discussed later in the SISTEr trial that

was conducted by the Urinary Incontinence Network, 47% of the Burch patients and 63% of the fascial sling patients had adverse events. (Albo ME, Burch colposuspension versus fascial sling to reduce urinary stress incontinence. N Engl J Med. 2007; 356:2143-55.)

The risks of SUI surgery include:

Damage to organs like the bladder

Ureteral injury

Damage to bowel

Damage to vessels

Damage to nerves

Anesthesia risks

Wound complications some requiring surgical intervention

Infection

Incisional hernia

Wound dehiscence (wound edge separation)

Seroma or hematoma

Granulation tissue or stitch granulations

Inflammation

Bleeding

Need for blood transfusion

Blood clot

DVT

Fistula

Erosion of suture (ie, into bladder)

Urinary tract infection (recurrent)

Recurrent cystitis (urinary bladder inflammation)

Catheter complications

Voiding dysfunction / difficulty

De novo detrusor overactivity

De novo urgency urinary incontinence

Urinary retention

Urinary frequency

Need for self-catheterization

Persistent Voiding dysfunction

Voiding dysfunction leading to surgical revision

Pain

Pain to the groin

Pelvic pain

Dyspareunia (Pain with sex)

Numbness or weakness from the surgery

Gastrointestinal problems

Bowel adhesion

Ileus / bowel obstruction.

Abdominal scar

Development of vaginal wall prolapse after Burch surgery

Need for repeat surgery

Urologists, Ob/Gyns and urogynecologists are trained on the risks of these surgeries in residency and fellowship. SUI surgery, including the TVT and TVT-O, are taught at many residencies and fellowship programs in the United States and Texas specifically. Mesh exposure/erosion is the only unique complication of the TVT and TVT-O as compared to other SUI surgeries. (FDA March 27, 2013 Statement, Considerations about Surgical Mesh for SUI; AUA October 2013 Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence). Moreover, colposuspension and fascial sling procedures rely on the use of permanent sutures, which can also lead to erosion, and wound complications also occur with these procedures. In particular the large abdominal incision is susceptible to wound herniation, seroma and infection and leads to scarring. Pain and nerve injury can also occur with the incision and secondary surgical site harvesting of fascia lata as well. Voiding dysfunction after SUI surgery, and associated with tensioning of sutures and biologic and synthetic slings, can occur with all SUI surgeries. Pain and dyspareunia can occur with all SUI surgeries, as can organ damage and bladder perforation. Knowledge of these risks is a basic part of female pelvic surgery training and from my standpoint as a medical doctor, these risks do not need to be incorporated into the TVT-O IFU. Surgeons would be aware of these risks from their basic training and experience.

Moreover these risks are obvious to pelvic floor surgeons performing SUI surgeries given the described surgical techniques and instruments and materials used during SUI surgery.

The Burch colposuspension procedure and the pubovaginal sling, using autologous rectus fascia, were studied in the SISTEr trial. (Albo ME., N Engl J Med. 2007;356:2143-55.) 520 of 655 women (79%) completed the outcome assessment. At 24 months, cumulative success rates were higher for women who underwent the fascial sling procedure than for those who underwent the Burch procedure, for both the overall category of success (47% vs. 38%, P=0.01) and the category specific to stress incontinence, which included no self-reported symptoms of stress incontinence, a negative stress test, and no retreatment for stress incontinence (66% vs. 49%, P<0.001).

Moreover, as reported in Figure 4, at 2 years the failure rate was 70% with the Burch and 57% for the sling in the overall category, and the failure rate for SUI specific criteria was 59% with the Burch and 40% with the fascial sling. Overall adverse events were higher with the fascial sling procedure (63% vs 49% in the Burch group) and more women in the fascial sling group had urinary tract infections, difficulty voiding, and postoperative urge incontinence. In the extended SISTEr trial, urinary continence rates decreased during a period of 2 to 7 years postoperatively from 42% to 13% in the Burch group and from 52% to 27% in the sling group, respectively. (Richter H, et al. Patient Related Factors Associated with Long-Term Urinary Continence After Burch

Colposuspension and Pubovaginal Fascial Sling Surgeries. J Urol. 2012; 188:485-9.) This study shows that rates with both procedures continue to decline over the longer term.

The TVT device was revolutionary in the field of SUI surgery. It was designed and developed by surgeons over many years of study. (Petros P. Creating a gold standard surgical device: scientific discoveries leading to TVT and beyond: Ulf Ulmsten Memorial Lecture 2014. Int Urogynecol J. 2015; 26:471-6.) Testing led to the development of the Integral Theory and numerous meshes such as Mersilene, Gore-Tex, Teflon and Marlex were tried in the device that would become the TVT, but with higher levels of erosion and tape rejection. (Petros PE, Ulmsten UI. An integral theory and its method for the diagnosis and management of female urinary incontinence. Scand J Urol Nephrol Suppl. 1993; 153:1-93; Ulmsten U, et al. An ambulatory surgical procedure under local anesthesia for treatment of female urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7:81-5; Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12 Suppl 2:S19-23.) Mersilene tape was found to induce a significant inflammatory reaction in paraurethral tissues, with a significant increase in collagen solubility by pepsin. (Falconer C, et al. Clinical outcome and changes in connective tissue metabolism after intravaginal slingplasty in stress incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 1996; 7:133-7.)

By 1996 the macroporous Prolene polypropylene mesh tape was found to be optimal for use in the TVT as a 1cm wide piece of tape covered by a protective sheath,

with high efficacy, low morbidity and low rates of mesh exposure. A tissue reaction study in women showed that there was proper tissue integration and minimal inflammatory reaction. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12 Suppl 2:S19-23.) The authors reported there was practically no tissue reaction at all seen 2 years after TVT surgery when Prolene mesh was used (Fig. 3), no tape rejections, and there was no change in collagen extractability in the Prolene group (Fig. 1). Additionally, there were no histological differences between paraurethral connective tissue in biopsies from patients operated on with Prolene tape and in controls 2 years after surgery. Lastly, there was no statistical difference in collagen concentration or extractability. Conversely, Mersilene showed two rejections, an intense inflammatory response, and a significant increase in collagen extractability by pepsin. By the time that TVT-O was released, the TVT had been successfully utilized in hundreds of thousands of patients, demonstrating high efficacy, a minimally invasive placement and low morbidity and complications. The TVT-O sling uses the same macroporous Prolene polypropylene mesh as the TVT.

Data cited in my report shows the macroporous Prolene polypropylene mesh tape used in the TVT and TVT-O to be universally accepted as the best material and most biocompatible for use in SUI. These include the highest levels of evidence such as Cochrane reviews, SUI Guidelines, systematic reviews and metaanalyses, and RCTs. Cochrane Reviews are systematic reviews of primary research in human health care and health policy, and are internationally recognized as the highest standard in evidence-

based health care. They investigate the effects of interventions for prevention, treatment and rehabilitation. (http://community.cochrane.org/cochrane-reviews)

For example the Ford 2015 Cochrane Review included 81 trials that evaluated 12,113 women the majority of which concerned the TVT and TVT-O devices. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. PMID: 26130017.) They found that MUS have been the most extensively researched surgical treatment for SUI in women and have a good safety profile. Irrespective of the routes traversed, they are highly effective in the short and medium term, and accruing evidence demonstrates their effectiveness in the long term. This review illustrates their positive impact on improving the quality of life of women with SUI. With the exception of groin pain which mostly resolved in the first 6 months, fewer adverse events occur with employment of a transobturator approach. The trials showed that over 80% of women with stress urinary incontinence are cured, or have significant improvement in their symptoms, with either operation, for up to five years after surgery. There is moderate quality evidence that overall reported rates of tape-related complications are low, such as erosion of the tape into the vagina at about 2% for both routes of tape insertion. The reported occurrence of problems with sexual intercourse including pain was low, and leakage of urine during intercourse are improved following insertion of these tapes.

At page 45, they also assessed complication rates derived from several registries involving thousands of patients, again the majority of whom received a TVT or TVT-O device, and reported low rates that were consistent with their primary analysis:

Event	**TVT**	**TVT-O / TOT**
Bladder perforation	2.7 - 3.9%	0.4%
Reoperation rates relating to tape insertion or voiding dysfunction	1.6 – 2.4%	0.8 – 2.2%
Urinary retention	1.6%	0.5%
Pelvic hematoma	0.7 – 1.9%	0.5%
Infection rate	0.7%	0.6%
Vaginal tape erosion / extrusion	1.5%	0.4%
Groin pain	0.4%	1.6%

Additionally, Ford reported that type 1 mesh like that in TVT and TVT-O:

> has the highest biocompatibility with the least propensity for infection. Differences in their efficacy and complications are likely to be due to several factors including the different knits and weaves of the various tape materials, their biomechanical properties and histological biocompatibility. Pore size affects the inflammatory response and resultant connective tissue formation within and into the mesh, and the rearrangement of materials such as collagen within the mesh structure. Macroporous meshes (pore size in excess of 75 μm) easily allow macrophages, leukocytes, fibroblasts, blood vessels and collagen to transverse the pores: thus macroporous meshes promote tissue host ingrowth with resultant biocompatibility and low risk of infection (Amid P. Classification of biomaterials and their related complications in abdominal wall hernia surgery. Hernia 1997; 1:15–21). Monofilament tapes are widely available and now predominate in current clinical practice.

As a result, macroporous, monofilament Prolene polypropylene mesh and the TVT and TVT-O have been specifically recommended for SUI treatment in light of the large body of data supporting the devices. (NICE (National Institute for Health and Care

Excellence) Clinical Guideline 171 - Urinary incontinence: The management of urinary incontinence in women, Sept. 2013). The NICE SUI Guideline recommends that when offering a synthetic mid-urethral tape procedure, surgeons should:

- use procedures and devices for which there is current high quality evidence of efficacy and safety [11]
- only use a device that they have been trained to use
- use a device manufactured from type 1 macro porous polypropylene tape
- consider using a tape coloured for high visibility, for ease of insertion and revision.

Footnote 11 referenced above states that the guideline only recommends the use of tapes with proven efficacy based on robust RCT evidence and identified TVT and TVT-O as meeting these criteria.

As noted above, the TVT and TVT-O include a macroporous (large pore > 75 microns), monofilament polypropylene mesh covered with a sheath that is attached to trocars / helical passers. The TVT is inserted via vaginal incision retropubically and the TVT-O is inserted via vaginal incision through the obturator (it is an "inside-out" transobturator passage). The sling is not anchored. Instead, tissue grows into the mesh and the mesh is held in place.

The sling works by providing support to the urethra, for example, when a woman coughs, sneezes or exercises. During TVT placement cystoscopy is performed to detect potential bladder perforation, a potential risk that is well known, warned of, and easy to manage intraoperatively. With the TVT-O, which passes through the obturator foramen, a cystoscopy is not needed, but surgeons are always free to perform one if they choose to do so. While plaintiffs' experts seem to take issue with blind passage of instruments,

similar procedures are used during the placement of an autologous sling. Moreover, the Burch colposuspension which is performed in an open manner can lead to bladder and bowel injury. (Schimpf MO, et al. Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71; AUA 2012 update to SUI Guidelines. https://www.auanet.org/common/pdf/education/clinical-guidance/Incontinence.pdf) Overall the rates of serious complications is less with TVT and TVT-O.

The sling is placed in the space between the vaginal wall and the urethra. When placed as described in the standard fashion, it does not traverse near the bladder or urethra. The mesh is taught to be placed tension-free at the midurethra with the aid of a blunt instrument between the urethra and sling, the sheath is removed, the ends are cut, the excess mesh is excised, and the small incisions are closed.

While plaintiffs' experts make claims about particle loss, I have not observed this clinically and even if particles were to get into the vagina, there would be no clinically significant effect. The particles are of the same Prolene polypropylene that make up the mesh. Moreover, Prolene polypropylene has long been used as a suture in various applications for decades. The clinical data on TVT and TVT-O also do not describe particle loss as playing any significant role on efficacy, which is high, or complications, which are low as discussed in my report. Also, during the surgery the site can be irrigated and suctioned, which would dispose of any particles. Their claims regarding

significant stretching of the mesh as seen on a machine in a lab leading to particle loss, mesh roping and curling are also not clinically significant. The mesh is not used in this manner clinically, as the bench testing removes the trocar, which provides a pathway for the mesh to traverse, and also removes the protective sheath. The protective sheath over the mesh bears the forces as the mesh is passed through the pelvis and as noted the mesh is placed tension free and spaced from the urethra with an instrument like a dilator before removing the sheaths. Also, surgeons do not pre-stretch the mesh to 50% elongation before placement of the TVT and TVT-O. Additionally, the mesh can be repositioned or replaced during the procedure. Mesh particles seen in packaging are also of no clinical concern for these reasons.

The macroporous Prolene polypropylene mesh cut to 1.1cm in width is a lightweight mesh in the TVT and TVT-O design application for the treatment of SUI. As noted in the January 2014 AUGS & SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence, "As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8]." Notably, reference 8 refers to the 17 year study of the TVT mesh. (Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013; 24:1265-69).

The Nilsson 17 year study of the TVT mesh demonstrated excellent efficacy over the long term and very low complications. Objective cure, defined as a negative stress test, was seen in 42 out of 46 women (91.3 %). Two of the women with a positive stress test were regarded as failures, while one woman considered herself significantly improved, even though she had minimal leakage at her stress test. 87.2 % regarded themselves cured or significantly better than before surgery and 50 out of 51 (98 %) would recommend the TVT procedure to a friend. The single tape complication seen during this prospective observational trial during a 17-year period was a small symptom-free exposure of the tape in a completely asymptomatic, continent and highly satisfied 69-year-old woman with an atrophic vaginal mucosa. She was prescribed local estrogen therapy. No other adverse effects, signs or reactions of the tape material could be detected among the women examined. These data have been replicated in several other studies assessing the TVT and TVT-O as discussed in my report.

The Nilsson 17 year study also showed that there was no shrinkage of the TVT mesh over time, as suggested by PVR volumes within normal ranges, except for 2 patients with concomitant diseases (Parkinson's, grade III cystocele). Similar data are seen in another prospective study where unchanged resting Q-tip angles confirm the tension-free concept of TVT and there was no shrinkage or tightening of the sling. (Lukacz ES, et al. The effects of the tension-free vaginal tape on proximal urethral position: a prospective, longitudinal evaluation. Int Urogynecol J Pelvic Floor Dysfunct. 2003; 14:179-84.) Other sling materials, such as cadaveric fascia, have been associated with significant tissue reaction and have been shown to shrink over time (Fokaefs ED, et

al. Experimental evaluation of free versus pedicled fascial flaps for sling surgery of urinary stress incontinence. J Urol 1997; 157:1039–1043). The authors noted that the TVT seems to be more elastic and associated with less tissue reaction than other materials. Falconer evaluated the TVT material in postoperative biopsy specimens from women undergoing the procedure and found minimal inflammation without a significant change in collagen solubility or significant foreign-body reaction. (Falconer C, et al. Influence of different sling materials on connective tissue metabolism in stress urinary incontinent women. Int Urogynecol J Pelvic Floor Dysfunct. 2001; 12 Suppl 2:S19-23.) Moreover, the low complication rates seen long term also contradict Plaintiff's experts' claims that the TVT mesh significantly contracts.

The TVT-O has been in use for almost 10 years now and the TVT sling has been in use for over 15 years now. It is my opinion that the TVT and TVT-O are the gold standard and current standard of care for the treatment of SUI. It is my opinion that the TVT and TVT-O are safe and effective. My opinions are supported by the major urologic and urogynecologic surgeon associations and societies. (NICE (National Institute for Health and Care Excellence) Clinical Guideline 171 - Urinary incontinence: The management of urinary incontinence in women, Sept. 2013; AUA Position Statement on the Use of Vaginal Mesh for the Surgical Treatment of Stress Urinary Incontinence, Oct. 2013; AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders, March 2013; AUGS & SUFU (Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction) Position Statement on Mesh Midurethral Slings for Stress Urinary Incontinence, Jan. 3, 2014; IUGA (International Urogynecological

Association) Position Statement on Mid-Urethral Slings for Stress Urinary Incontinence, July 2014; Schimpf MO, et al. Society of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71.).

The AUA October 2013 Statement, which I agree with, concluded that:

> Suburethral synthetic polypropylene mesh sling placement is the most common surgery currently performed for SUI. Extensive data exist to support the use of synthetic polypropylene mesh suburethral slings for the treatment of female SUI, with minimal morbidity compared with alternative surgeries. Advantages include shorter operative time/anesthetic need, reduced surgical pain, reduced hospitalization, and reduced voiding dysfunction. Mesh-related complications can occur following polypropylene sling placement, but the rate of these complications is acceptably low. Furthermore, it is important to recognize that many sling-related complications are not unique to mesh surgeries and are known to occur with non-mesh sling procedures as well. It is the AUA's opinion that any restriction of the use of synthetic polypropylene mesh suburethral slings would be a disservice to women who choose surgical correction of SUI. Additionally, both the Society of Urodynamics, Female Pelvic Medicine and Urogenital Reconstruction (SUFU) and the AUA support the use of multi-incision monofilament midurethral slings for the treatment of SUI in properly selected patients who are appropriately counseled regarding this this surgical procedure by surgeons who are trained in the placement of such devices, as well as the recognition and management of potential complications associated with their use.
>
> Multiple case series and randomized controlled trials attest to the efficacy of synthetic polypropylene mesh slings at 5-10 years. This efficacy is equivalent or superior to other surgical techniques. There is no significant increase in adverse events observed over this period of followup. Based on these data, the AUA Guideline for the Surgical Management of Stress Urinary Incontinence (2009) concluded that synthetic slings are an appropriate treatment choice for women with stress incontinence, with similar efficacy but less morbidity than conventional nonmesh sling techniques.

The March 2013 AUGS Position Statement similarly concluded based on high level evidence that full-length midurethral slings, both retropubic and transobturator,

have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard of care for stress incontinence surgery.

In 2014, SUFU which has over 500 members, and AUGS which has over 1,700 members, issued a Position Statement which analyzes high level data including level 1 Cochrane Review, RCTs and long term study of the TVT mesh and discusses the acceptance and utility of the TVT and TVT-O midurethral slings. They observe that "The polypropylene mesh midurethral sling is the recognized worldwide standard of care for the surgical treatment of stress urinary incontinence. The procedure is safe, effective, and has improved the quality of life for millions of women." I am in agreement with this statement.

My review of the literature and clinical experience are consistent with their conclusion and the basis for the conclusion, and with which I agree:

Justification for the Position Statement

1. Polypropylene material is safe and effective as a surgical implant.

Polypropylene material has been used in most surgical specialties (including general surgery, cardiovascular surgery, transplant surgery, ophthalmology, otolaryngology, gynecology, and urology) for over five decades, in millions of patients in the US and the world (personal communication with manufacturers of polypropylene suture and mesh). As an isolated thread, polypropylene is a widely used and durable

suture material employed in a broad range of sizes and applications. As a knitted material, polypropylene mesh is the consensus graft material for augmenting hernia repairs in a number of areas in the human body and has significantly and favorably impacted the field of hernia surgery. [6, 7] As a knitted implant for the surgical treatment of SUI, macroporous, monofilament, light weight polypropylene has demonstrated long term durability, safety, and efficacy up to 17 years [8].

2. The monofilament polypropylene mesh MUS is the most extensively studied anti-incontinence procedure in history.

A broad evidence base including high quality scientific papers in medical journals in the US and the world supports the use of the MUS as a treatment for SUI [9]. There are greater than 2000 publications in the scientific literature describing the MUS in the treatment of SUI. These studies include the highest level of scientific evidence in the peer reviewed scientific literature [9]. The MUS has been studied in virtually all types of patients, with and without comorbidities, and all types of SUI. Multiple randomized, controlled trials comparing types of MUS procedures, as well as comparing the MUS to other established non-mesh SUI procedures, have consistently demonstrated its clinical effectiveness [9-12] and patient satisfaction [12]. Among historical SUI procedures, the MUS has been studied as long in follow-up after implantation as any other procedure and has demonstrated superior safety and efficacy [8]. No other surgical treatment for SUI before or since has been subject to such extensive investigation.

3. Polypropylene mesh midurethral slings are the standard of care for the surgical treatment of SUI and represent a great advance in the treatment of this condition for our patients.

Since the publication of numerous level one randomized comparative trials, the MUS has become the most common surgical procedure for the treatment of SUI in the US and the developed world. This procedure has essentially replaced open and transvaginal suspension surgeries for uncomplicated SUI. There have been over 100 surgical procedures developed for the management of SUI and there is now adequate evidence that the MUS is associated with less pain, shorter hospitalization, faster return to usual activities, and reduced costs as compared to historic options that have been used to treat SUI over the past century. Full-length midurethral slings, both retropubic and transobturator, have been extensively studied, are safe and effective relative to other treatment options and remain the leading treatment option and current gold standard for stress incontinence surgery [13]. Over 3 million MUS have been placed worldwide and a recent survey indicates that these procedures are used by > 99% of AUGS members [14].

4. The FDA has clearly stated that the polypropylene MUS is safe and effective in the treatment of SUI.

The midurethral sling was not the subject of the 2011 FDA Safety Communication, “Urogynecologic Surgical Mesh: Update on the Safety and Effectiveness of Vaginal Placement for Pelvic Organ Prolapse.”[3]. In this document, it was explicitly

stated: “The FDA continues to evaluate the effects of using surgical mesh for the treatment of SUI and will report about that usage at a later date.” In 2013, the FDA website stated clearly that: “The safety and effectiveness of multi-incision slings is well-established in clinical trials that followed patients for up to one-year.” [5].

Conclusion: The polypropylene midurethral sling has helped millions of women with SUI regain control of their lives by undergoing a simple outpatient procedure that allows them to return to daily life very quickly. With its acknowledged safety and efficacy it has created an environment for a much larger number of women to have access to treatment. In the past, concerns over failure and invasiveness of surgery caused a substantial percent of incontinent women to live without treatment. One of the unintended consequences of this polypropylene mesh controversy has been to keep women from receiving any treatment for SUI. This procedure is probably the most important advancement in the treatment of stress urinary incontinence in the last 50 years and has the full support of our organizations which are dedicated to improving the lives of women with urinary incontinence.

IUGA, which represents surgeons practicing around the world, has also analyzed the high level data on polypropylene midurethral slings and in particular TVT and TVT-O. It is important to note that the vast majority of high level data are on the TVT and TVT-O device, as they have the most randomized controlled trials and longest follow up and the studies, RCTs, Cochrane reviews and metaanalyses cited by IUGA in their analysis involve TVT and TVT-O. IUGA found that:

> Mid-urethral slings are minimally invasive procedures developed in Europe in the 1990s to treat female stress urinary incontinence. These slings are narrow, synthetic polypropylene tapes that are surgically placed beneath the middle part of the urethra (water pipe) to provide dynamic support to stop leakage from the bladder. They have been shown to be as effective as more invasive traditional surgery with major advantages of shorter operating and admission times, and a quicker return to normal activities together with lower rates of complications.[3] This has resulted in MUS becoming the operation of choice in Europe, Asia, South America, South Africa, Australasia[4] and North America[5] for treatment of SUI with several million procedures performed worldwide.
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> (Cody J, et al. Systematic review of the clinical effectiveness and cost-effectiveness of tension-free vaginal tape for treatment of urinary stress incontinence. Health Technol Assess 2003; 7:iii, 1–189.; Lee J, Dwyer PL. Age related trends in female Stress Urinary Incontinence Surgery in Australia – Medicare data 94 – 09. Aust N Z J Obstet Gynaecol 2010; 50:543-49 PMID:21133865; http://www.augs.org/d/do/2535.)

IUGA's analysis of numerous Level 1 Cochrane reviews and a meta-analysis determined that "There is robust evidence[9-11] to support the use of MUS from over 2,000 publications making this treatment the most extensively reviewed and evaluated procedure for female stress urinary incontinence now in use. These scientific publications studied all types of patients, including those with co-morbidities such as prolapse, obesity and other types of bladder dysfunction." (Ogah J, Cody JD, & Rogerson L. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst. Rev. CD006375 (2009); Rehman H, Bezerra CC, Bruschini H, Cody JD. Traditional suburethral sling operations for urinary incontinence in women. Cochrane Database Syst. Rev. CD001754 (2011); Novara, G., et al., Updated systematic review and meta-analysis of the comparative data on

colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol, 2010. 58(2): p. 218-38.)

The TVT and TVT-O slings are taught to residents, fellows and surgeons and in a recent study involving 53 expert urologists and urogynecologists (of whom >90% were fellowship trained) and who could select among many surgical options, the full-length synthetic midurethral sling was the preferred option in 93% for the surgical treatment of primary stress incontinence. (Nager, C.W., et al., A randomized trial of urodynamic testing before stress-incontinence surgery. N Engl J Med 2012; 366:1987-97.) These data are consistent with a recent study carried out in December 2011 that assessed AUGS members' usage of mesh slings, which showed that more than 99% used them before the July 13, 2011 FDA safety update and 96% used them after. (Clemons JL, et al., Impact of the 2011 FDA transvaginal mesh safety update on AUGS members' use of synthetic mesh and biologic grafts in pelvic reconstructive surgery. Female Pelvic Med Reconstr Surg 2013; 19:191-98.) The TVT and TVT-O are safe and effective, easy to teach and learn, and are backed by reams of data, making it the first-line treatment for SUI.

This is also consistent with a study that analyzed case data logs for female incontinence surgeries in 4,185 certifying and recertifying urologists from the American Board of Urology and showed that midurethral slings have been widely adopted by urologists over the last decade. Study data revealed that while traditional procedures decreased from 17% of female incontinence procedures in 2003 to 5% in 2004 to <1%

since 2010 (P <.0005), urologists were using more midurethral slings over the same period -- from 3210 procedures in 2003 to 7200 in 2012 (P <.0005). (Chughtai BI, et al. Midurethral sling is the dominant procedure for female stress urinary incontinence: analysis of case logs from certifying American Urologists. Urology. 2013; 82:1267-71.)

This echoed by the International Continence Society, which includes members from across the world, in their 2013 Stress Urinary Incontinence Fact Sheet, which states "Definitive therapy for SUI is surgical and involves restoring urethral support through use of a sling. Worldwide, midurethral slings comprised of synthetic mesh have become the treatment of choice for SUI. Long-term data are robust and demonstrate durable efficacy with a very low complication rate, particularly in experienced hands."

As noted earlier, the NICE Clinical Guideline specifically recommends the TVT and TVT-O as suitable first line surgical options because of their robust and high quality evidence. The European Association of Urology also endorses the midurethral sling as the first line treatment option, with which I agree because of its well established safety and effectiveness. (Lucas MG, EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012; 62:1118-29). The TVT and TVT-O are minimally invasive and less invasive than other surgical options, such as the Burch and native tissue sling.

The Ogah 2009 and 2011 Cochrane Reviews assessed 62 trials involving 7,101 women. Minimally invasive synthetic slings like TVT and TVT-O appeared to be as effective as traditional suburethral slings, but with shorter operating time, and less post-operative voiding dysfunction and de novo urgency symptoms. Midurethral sling

operations were as effective as open retropubic colposuspension with fewer perioperative complications, less postoperative voiding dysfunction, and shorter operative time and hospital stay, but the TVT had significantly more bladder perforations. (Ogah J, et al. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD006375; Ogah J, et al. Minimally invasive synthetic suburethral sling operations for stress urinary incontinence in women: a short version Cochrane review. Neurourol Urodyn. 2011; 30:284-91).

In the Ogah Cochrane Review, monofilament tapes like TVT and TVT-O had higher cure rates compared to multifilament tapes, and fewer tape erosions (1.3% versus 6%). TVT was more effective than top-to-bottom route and incurred significantly less voiding dysfunction, bladder perforations, and tape erosions. No statistically significant difference was found between retropubic and transobturator slings, with patients in both groups reporting an 83% success rate. Objective cure rates at 12 months for 2,434 patients slightly favored TVT (88% versus 84%.) Although statistically significant, this difference is not clinically significant. The Review concluded that current evidence suggested that minimally invasive synthetic suburethral sling operations like TVT and TVT-O are as effective as traditional suburethral slings, open retropubic colposuspension and laparoscopic colposuspension in the short term but with fewer postoperative complications. These data are consistent with the European Association of Urology's recent recommendation of the midurethral sling as a first line surgical option for SUI; it is effective, less invasive, and patients recover more quickly. (Lucas

MG, EAU Guidelines on Surgical Treatment of Urinary Incontinence. Eur Urol. 2012;62:1118-29.)

In November 2015, ACOG and AUGS issued Practice Bulletin 155 – Clinical Management Guidelines concerning Urinary Incontinence in Women. (Urinary incontinence in women. Practice Bulletin No. 155. American College of Obstetricians and Gynecologists. Obstet Gynecol 2015; 126:e66–81.) The purpose of the document was to review information on the current understanding of urinary incontinence in women and to outline guidelines for diagnosis and management that are consistent with the best available scientific evidence. ACOG and AUGS analyzed data and made the following conclusions and practice recommendations to gynecologists and pelvic surgeons, which based on Level A good and consistent scientific evidence, establish that TVT and TVT-O are effective, safe, less invasive than alternatives, and a first line SUI surgery:

- Synthetic midurethral slings demonstrate efficacy that is similar to traditional suburethral fascial slings, open colposuspension, and laparoscopic colposuspension. Compared with suburethral fascial slings, fewer adverse events have been reported with synthetic midurethral slings. Voiding dysfunction is more common with open colposuspension than with synthetic midurethral slings.
- There are substantial safety and efficacy data that support the role of synthetic mesh midurethral slings as a primary surgical treatment option for stress urinary incontinence in women.
- Burch colposuspension at the time of abdominal sacrocolpopexy and retropubic midurethral sling at the time of vaginal surgery for pelvic organ prolapse repair

decrease the risk of postoperative stress urinary incontinence in women without preoperative stress urinary incontinence.

Tan conducted a recent meta-analysis of 40 RCTs (minimum duration 12 months) that compared TVT, TVT-O and TOT. (Tan PF, et al. Effectiveness and complication rates of tension-free vaginal tape, transobturator tape, and tension-free vaginal tape-obturator in the treatment of female stress urinary incontinence in a medium- to long-term follow up. Meta-analysis of randomized controlled trials. Saudi Med J. 2014; 35:20-32.) TVT and TVT-O were found to have similar objective and subjective cure rates. The TVT had a higher risk of bladder perforation than TVT-O, and a lower risk of groin/thigh pain than TOT. TVT-O had a lower risk of vaginal erosion than TOT and TOT also had a significantly higher reoperation rate than TVT-O.

The TVT-O and TVT have been studied extensively over the past 15 years and there are numerous 5 and 10+ year studies such as these below that demonstrate their safety and efficacy:

Study & Duration	**# Pts.**	**Objective Success**	**Subjective Success**	**Other**
Nilsson 2008 (11 years follow up)	69	90%	77% felt cured and 20% were improved.	93% no leakage on straining. 97% would recommend TVT to a friend.
Liapis 2008 (7 years follow up)	61	80% and 6.5% improved.	78.7% felt cured and 8.1% improved.	
Olsson 2010 (11.5 yrs follow up)	124	84%	77% felt cured and 18% improved.	94% were satisfied (74% very satisfied and 20% satisfied).

Study & Duration	**# Pts.**	**Objective Success**	**Subjective Success**	**Other**
Groutz 2011 (10 years follow up)	52	N/A	65% felt cured and 12% improved.	
Aigmueller 2011 (10 years follow up)	141	84% and 8.5% were slightly positive.	57% felt cured and 23% improved.	
Heinonen 2012 (10.5 yrs follow up	138	90%	78%	
Serati 2012 (10 years follow up)	58	93.10%	89.7% satisfied and 93.1% were improved.	91.4% urodynamic cure rate
Nilsson 2013 (17 years follow up)	58	91.30%	87.2% felt cured or significantly better.	98% would recommend TVT to a friend.
Svenningsen 2013 (10.75 yrs follow up)	483	89.90%	76.1% felt cured and 18% were better. (94.1% improved).	82.6% stated they were very satisfied.
Liapis 2010 (TVT-O 4 years follow up)	115	82% and 7% were improved.	81% cure and 9.4% improvement.	Cough stress test objective cure: TVT-O 85.1% and TVT-O + Ant. Colp. 82.9%.
Angioli 2010 (TVT-O 5 years follow up)	31	73% (89.2% negative cough stress test)	62% reported satisfied or very satisfied.	78.4% would undergo again. Significant improvement in patient satisfaction per VAS scores.
Groutz 2011 (TVT-O 5 years follow up)	61	N/A	N/A	74% cured based on a composite negative CST, no SUI episodes, and positive global satisfaction. An additional 8% were improved.

Study & Duration	**# Pts.**	**Objective Success**	**Subjective Success**	**Other**
Cheng 2012 (TVT-O 5.4 years follow up)	100	92%	90.00%	Significant improvement in QOL at 1- and 5-year follow up.
Serati 2013 (TVT-O 5 years follow up)	185	90.80%	90.30%	
Laurikainen 2014 (TVT-O 5 years follow up, RCT)	123	86.20%	85.6% and an additional 6.1% expectations partly met	88.6% would recommend to a friend. Significant improvement in all QOL scores.
Athanasiou 2014 (TVT-O 7.5 years follow up)	124	81.50%	83.5% and an additional 3.2% were improved.	Significant QOL improvement. Objective and subjective cure rates in TVT-O only group 90.3% (28/31).

Recently, Tommaselli published a systematic review and metaanalyses of medium and long term studies, 49 in total, concerning midurethral slings. (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015; 26:1253-68.) Notably TVT and TVT-O represented the vast amount of data as they were represented in 43 of the 49 studies (Tables 1 and 2). With regard to patient numbers, Table 3 reports that there were 3,974 retropubic (TVT = 3,801) and 2,432 transobturator (TVT-O = 1,375) patients. High objective and subjective cure rates in the long- and medium-term were seen. TVT-O was associated with a significantly lower incidence of vaginal injuries than TOT. There was no difference in persistent pain,

defined as all pain reported beyond the perioperative period (>7 days after procedure), between RP-MUS and TO-MUS (2.2 % vs. 1.9 %). Persistent or chronic pain (i.e. pain persisting beyond the perioperative period or reported at the last follow-up visit) was very rare and reported by 13 patients for RP-MUS (13/3,974 = 0.3%) and 30 patients for TOMUS (30/2,432 = 1.2%). The authors concluded that RPMUS and TO-MUS have similar objective cure rates in the long-term and medium-term but TOTs have a lower subjective cure rate than TVT. This efficacy is backed by a high safety profile, and by a limited number of complications which were seldom severe.

In comparison, in a study including 190 women who underwent open Burch colposuspension, significant urinary incontinence was observed in 56% of patients and only 19% of women remained completely dry at 14 years follow up. (Kjolhede, P, et al. Long-term efficacy of Burch colposuspension: a 14-year follow-up study. Acta Obstet. Gynecol. Scand. 2008;84:767–72). Another study of the Burch reported a cure rate of 69%, 15% de novo detrusor instability and 24 patients (22 %) still complained of voiding difficulty 10 years or more after the colposuspension with four undergoing urethrotomy. (Alcalay M, et al. Burch colposuspension: a 10-20 year follow up. Br J Obstet Gynaecol. 1995; 102:740-5). Though, this study was limited by over 60% loss to follow up.

In a study assessing the Burch in 65 women prospectively at 1.5 years and 155 women retrospectively 4.5 years follow up, cure declined from 87.7% to 77.4%. (Demirci F, et al. Long-term results of Burch colposuspension. Gynecol Obstet Invest. 2001; 51:243-7.) The symptom-free cure rate declined 83.9% for 3, 76.2% for 4, 75% for 5 and

68% for 6 years. Demirci reported several other studies that also tended to show that cure with the Burch declined over time comparable to their results:

- Van Geelen et al. [5] reported an objective cure rate after 3 months of 100% and at 1-2 years it was 85%. However, 5 years after the procedure only 75.8% of the women were symptom-free. (van Geelen JM, et al. The clinical and urodynamic effects of anterior vaginal repair and Burch colposuspension. Am J Obstet Gynecol 1988; 159:137-144.)

- Thunedborg et al. [6] reported a complete cure rate of 78.6% for 6 years. (Thunedborg P, et al. Stress urinary incontinence and posterior bladder suspension defects. Results of vaginal repair versus Burch colposuspension. Acta Obstet Gynecol Scand 1990; 69:55-59.)

- Kinn [9] reported 78% for 5 years. (Kinn AC: Burch colposuspension for stress urinary incontinence. Scand J Ural Nephrol 1995; 29:449-455.)

- Eriksen et al. [8] reported 67% for 5 years. (Eriksen BC, et al. Long-term effectiveness of the Burch colposuspension in female urinary stress incontinence. Acta Obstet Gynecol Scand 1990; 69:45-50.)

- Lebret et al. [10] reported 64% for 5 years. (Lebret T, et al. Isolated Burch type indirect colposuspension of the bladder neck in the treatment of stress urinary incontinence in women. Long-term results. Prog Urol 1997; 7:426-432.)

- Kjolhede and Ryden [11] reported 63% for 6 years. (Kjolhede P, Ryden G. Prognostic factors and long-term results of the Burch colposuspension. Acta Obstet Gynecol Scand 1994; 73:642-647.)

- Christensen et al. [12] reported 33%. (Christensen H, et al. Long-term result of the Stamey bladder neck suspension procedure and of the Burch colposuspension. Scand J Ural Nephrol 1997; 31:349-353.)

As noted above, late complications can occur with the Burch and Demirci reported that at follow up, late complications in the 220 women included dyspareunia in 6, groin or suprapubic pain in 15, cystocele in 18, rectocele in 32 and enterocele in 35.

In a long term RCT of TVT versus the laparoscopic Burch procedure, incontinence rates were similar (57% had subjective urinary incontinence after laparoscopic Burch colposuspension versus 48% after TVT) and 11% of the laparoscopic Burch group and 8% of the TVT group had bothersome SUI. (Jelovsek JE, et al. Randomised trial of laparoscopic Burch colposuspension versus tension-free vaginal tape: long-term follow-up. BJOG. 2008; 115:219–225.)

In a recent multi-center study, initial midurethral-sling surgery including TVT and TVT-O resulted in higher rates of subjective improvement and subjective and objective cure at 1 year when compared with initial physiotherapy involving pelvic-floor muscle training. (Labrie J, et al. Surgery versus physiotherapy for stress urinary incontinence. N Engl J Med. 2013; 369:1124-33.) The study noted that midurethral-sling surgery is a minimally invasive surgical technique for the treatment of stress urinary incontinence with subjective cure rates between 75% and 94% and objective cure rates between 57% and 92%. The procedure is regarded as effective, with minimal complications. A recent well done review of the literature reports numerous high level data which shows the TVT and TVT-O have been significantly studied, are safe and effective, and have acceptable complication rates in my opinion. (Cox A, et al. Surgical management of female SUI: is there a gold standard? Nat Rev Urol. 2013; 10:78-89.)

A large meta-analysis of numerous RCTs comparing the TVT to other SUI surgeries found that the TVT outperformed the Burch colposuspension in terms of postoperative continence rates and success rates were similar after TVT and

pubovaginal slings. (Novara G, et al. Tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials of effectiveness. Eur Urol 2007; 52:663-678.) Similar objective and subjective cure rates were shown between TVT and TVT-O.

The following year, the group performed another meta-analysis which showed lower rates of reoperation for TVT compared to Burch, TVT had more bladder perforations than Burch, and there were similar complications to pubovaginal slings. (Novara G, et al. Complication rates of tension-free midurethral slings in the treatment of female stress urinary incontinence: a systematic review and meta-analysis of randomized controlled trials comparing tension-free midurethral tapes to other surgical procedures and different devices. Eur Urol. 2008; 53:288-308.) In Table 6 of the study, an analysis of over 30 TVT studies, each with a follow up of more than 2 years, showed acceptable rates for complications (the cumulative rates were 1.7% for pelvic hematoma, 3.4% for bladder perforations, 1.1% for vaginal erosion, 0.8% for bladder erosion, 9.7% for urinary tract infections, 15.6% for storage LUTS, 16.1% for voiding LUTS, 4% for clean intermittent catheterization, and 3.2% for reoperations).

More recently, they conducted a meta-analysis of 39 RCTs, which showed that patients receiving midurethral tapes including TVT-R, which was the most studied midurethral sling, and TVT-O, had significantly higher overall and objective cure rates than those receiving Burch colposuspension, although they had a higher risk of bladder perforations. Patients undergoing midurethral tapes and pubovaginal slings had similar

cure rates, although the pubovaginal sling patients were slightly more likely to experience storage lower urinary tract symptoms and had a higher reoperation rate. Retropubic tapes had a slightly higher objective cure rates than the transobturator tapes and subjective cure rates were similar. (Novara G, et al. Updated systematic review and meta-analysis of the comparative data on colposuspensions, pubovaginal slings, and midurethral tapes in the surgical treatment of female stress urinary incontinence. Eur Urol. 2010; 58:218–38.)

A meta-analysis comparing TVT-O to TOT found an equal rate of both subjective and objective success rates. Bladder injury and voiding difficulties were less frequent with the TVT-O than the TOT. (Latthe PM, et al. Two routes of transobturator tape procedures in stress urinary incontinence: a meta-analysis with direct and indirect comparison of randomized trials. BJU Int 2010; 106:68–76).

The TVT and TVT-O are also effective in cases of mixed incontinence. A systematic review and meta-analysis of six randomized controlled trials and seven prospective non-randomized studies including women with symptomatic and/or urodynamic mixed urinary incontinence showed persistent and good cure of stress component following midurethral sling surgery and cure of the urge component was variable but less than the stress component. (Jain P, et al. Effectiveness of midurethral slings in mixed urinary incontinence: a systematic review and meta-analysis. Int Urogynecol J. 2011; 22:923–932.) The cure rate of SUI following MUS was between 85%

and 97%. The overall cure of urgency and UUI component was 30-85% at a follow-up of few months up to 5 years.

The TVT and TVT-O have also shown to be effective in patients with SUI and overactive bladder (OAB). In a prospective multicenter study comparing TVT and TVT-O in treating OAB symptoms using validated objective and subjective measures in women with both SUI and OAB, both TVT and TVT-O resulted in significant improvement in OAB symptoms. (Han JY, Effectiveness of retropubic tension-free vaginal tape and transobturator inside-out tape procedures in women with overactive bladder and stress urinary incontinence. Int Neurourol J. 2013; 17:145-51.) The mean number of urgency episodes per 24 hours decreased in both groups. The overall objective cure rates for SUI were 95.2% with TVT and 92.2% in the TVT-O group. Subjective cure rates for SUI were 85% with TVT and 79.6% in the TVT-O group. All subscales of BFLUTSSF (voiding, filling, incontinence, sexual function, and quality of life (QoL)) were improved in both groups, but the improvement in QoL was significantly higher in the TVT group (P=0.002). In both groups, urination frequency and nocturia as well as urgency and urgency urinary incontinence (UUI) symptoms were significantly improved after surgery. The cure rates for urgency (53% for TVT vs. 51% for TVT-O) and UUI (55% for TVT vs. 52% for TVT-O) did not differ significantly between the two groups. After surgery, the urgency perception scale (UPS) was also significantly improved. The rates of patient satisfaction were similar at 95.2% in the TVT group and 96.7% in the TVT-O group.

In Laurikainen's five year RCT of TVT (n=131) versus TVT-O (n=123), new-onset urgency incontinence was seen in <3% of the women compared to 80% of the women with preoperative urgency symptoms were relieved of these symptoms 5 years later. (Laurikainen E, et al. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014; 65:1109-14.) These findings suggest that the risk of developing urgency symptoms with or without leakage after TVT and TVT-O is very low and that actually, as discussed earlier, TVT and TVT-O surgery can cure urgency symptoms and is effective in mixed incontinence. (Palva K, Nilsson CG. Prevalence of urinary urgency symptoms decreases by mid-urethral sling procedures for treatment of stress incontinence. Int Urogynecol J 2011; 22:1241–7; Abdel-Fattah M, et al. Evaluation of transobturator tension-free vaginal tapes in surgical management of mixed urinary incontinence: 3-year outcomes of a randomized controlled trial. J Urol 2014; 191:114–9.). Similarly, another study in women with urodynamically proven stress incontinence and detrusor overactivity who had failed conservative treatment showed a significant reduction in SUI and OAB symptoms (urge urinary incontinence ($p<0.001$), urgency ($p=0.021$) and frequency ($p=0.014$)) after treatment with TVT and TVT-O. (Athanasiou S, et al. Midurethral slings for women with urodynamic mixed incontinence: what to expect? Int Urogynecol J. 2013; 24:393-9.)

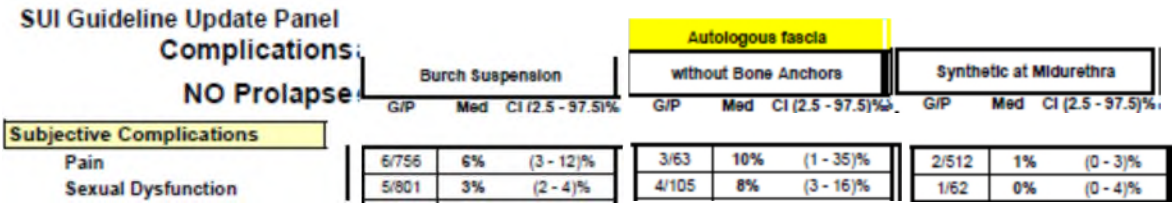
Sexual activity and function are not negatively impacted by TVT or TVT-O. This is consistent with the recent systematic review and meta-analysis by the Society of Gynecologic Surgeons Systematic Review Group which stated that dyspareunia was rare with the retropubic (<0.001%) and obturator (0.16%) slings. (Schimpf MO, et al. Society

of Gynecologic Surgeons Systematic Review Group. Sling surgery for stress urinary incontinence in women: A systematic review and meta-analysis. Am J Obstet Gynecol. 2014; 211:71.e1-71.) Overall the rates were lower than for the pubovaginal sling:

TABLE 3
Rates of AEs by sling type analyzed from randomized controlled trials and included AE studies[1,9-57,59-117]

Sling category	Studies	Summary estimate of incidence (95% CI)	Events	Total n	Range of AE proportions across studies
Dyspareunia					
Retropubic	2	0.00% (0.01–1.64%)	0	488	0.00–0.00%
Obturator	6	0.16% (0.02–1.14%)	1	624	0.00–0.40%
Minisling	11	0.74% (0.40–1.2%)	19	1809	0.00–6.49%
Pubovaginal	5	0.99% (0.39–1.9%)	8	696	0.00–2.63%

Similarly, in the AUA 2012 update to the SUI Guidelines, pain and sexual dysfunction were higher with the Burch and autologous sling than the midurethral sling:



The Urinary Incontinence Treatment Network conducted a large, multi-center randomized controlled trial of 597 women with SUI undergoing TVT compared with transobturator midurethral slings (there were 161 TVT-O patients and 137 TOT patients) and assessed sexual activity and function. (Zyczynski HM, et al. Sexual activity and function in women more than 2 years after midurethral sling placement. Am J Obstet Gynecol 2012; 207:421.e1-6. (TOMUS study)). The study participants were predominantly white (79.2%), middle-aged (52.9 ± 11.0 years), and obese (BMI 30.3 ± 6.7 kg/m2).

Significant, similar improvements in sexual function were seen in both midurethral sling groups. Mean PISQ (Pelvic Organ Prolapse/Urinary Incontinence Sexual Questionnaire) scores increased from 32.8 at baseline to 37.6 at 6 months and 37.3 at 24 months (P<.0001). Dyspareunia, incontinence during sex, and fear of incontinence during sex each significantly improved after surgery. Specifically, pain with intercourse was reported by 153 of 406 of sexually active women (38%) at baseline and decreased to 27% at 12 months after surgery (P= .003). Self-reported urge incontinence and the fear that incontinence might occur during sexual activity also significantly improved by 12 months after surgery, regardless of sling route (P < .0001 for both). Neither intra-operative nor postoperative complications were associated significantly with sexual activity or function. To investigate the association of synthetic mesh slings with dyspareunia, the study authors repeated the analysis on the 247 women who underwent MUS only (no concurrent procedures) and who completed baseline and 12-month assessments. The positive effect of TVT and TVT-O on dyspareunia were again seen. In this subset of women, dyspareunia decreased from 57% at baseline to 43% at 12 months after surgery (P = .03). Preoperative urge incontinence was associated with abstinence after surgery (P =.02). Postoperative urge incontinence was associated with diminished sexual function as measured by PISQ-12 (P=.047), but did not affect frequency of self-reported sexual activity.

Similarly, in a 12 month study, sexual function was found to improve in women with urodynamic stress incontinence (USI) and intrinsic sphincter deficiency (ISD). A significant increase was detected in PISQ-12 score following both TVT and Monarc

insertion. This score was greater in the TVT group at 6 months but not at 12 months when compared to the Monarc group. A significant decrease in UDI-6 and IIQ-7 score was detected. Specifically, coital incontinence and fear of leakage were reduced in both groups, and no change in dyspareunia or orgasm intensity was found. (De Souza A, et al. Sexual function following retropubic TVT and transobturator Monarc sling in women with intrinsic sphincter deficiency: a multicentre prospective study. Int Urogynecol J. 2012 Feb;23:153-8.)

Patient satisfaction was also assessed across numerous parameters in the TOMUS trial. (Wai CY, et al. Patient Satisfaction After Midurethral Sling Surgery for Stress Urinary Incontinence. Obstet Gynecol 2013;121:1009–16) Both the TVT and TVT-O groups demonstrated a high level of satisfaction in patients with respect to urine leakage (retropubic 85.9% compared with transobturator 90.0%), urgency to urinate, frequency of urination, capability of physical activity, social activity, ability to engage in sexual activity, and from an emotional standpoint. A very telling point is that more than 95% of participants in both sling groups indicated that they would still choose to have the surgery or recommend it to a family member or friend if they could go back in time with the knowledge and experience they acquired after the surgery.

Other studies have shown the TVT and TVT-O to be safe and effective in overweight and obese. In a meta-analysis of seven TVT studies including 453 obese and 1186 non-obese patients, good cure rates were shown in the obese group (81%) and the non-obese group (85%). (Greer WJ, et al. Obesity and pelvic floor disorders: a

systematic review. Obstet Gynecol. 2008;112:341-9.) Although statistically significant, the difference is not clinically significant.

Outcomes of the TVT® procedure in the obese

Study	N (Obese / Nonobese)	Follow-up (months)	% Cure (Obese / Nonobese)	*P* value	Complications
Mukherjee et al (26), 2001	87 / 156	Not given	90 / 91.2	NS	No difference in urinary retention, operative complications
Chung et al (32), 2002	60 / 31	(12 -24)	100 / 100	NS	No difference in length of hospital stay, voiding dysfunction
Rafii et al (31), 2003	39 / 149	27 (6 - 38)	82 / 91.2	0.1	More persistent urge UI in obese (17.9% vs. 4.6%)
Lovatsis et al (28), 2003	35 / 35	(6 – 24)	88.6 / 91.4	NS	- More bladder perforations in nonobese (14 vs. 0%, *P* = 0.03) - Longer operative time in obese (49 vs. 35 min, *P* < 0.05)
Skriapas et al (27), 2005	31 / 52	18.5 (12 – 24)	87 / 92	0.103	More early postoperative complications in obese (48.4% vs. 38.5%, *P* = 0.021)
Ku et al (33), 2006	45 / 240	10	84.4 / 91.6	0.173	No difference in urinary retention, persistent urgency
Hellberg et al (30), 2006	163 / 570	68.4 (24 – 96)	66.1 / 77.5	*	* Cure rates for BMI < 25 = 81%, for BMI > 35 = 52.1% (*P* = 0.0005)

The rate of bladder perforation was also assessed in the meta-analysis and the results did not show an increased risk in the obese patients as combined bladder perforation rates were 1.2% in the obese and 6.6% in the non-obese.

More recently, another paper showed that overweight and obese women undergoing TVT and TVT-O have good cure rates and the procedure is safe. (Osborn DJ, et al. Obesity and female stress urinary incontinence. Urology. 2013;82:759-63.) Several studies were included on this point and overall the subjective and objective cure rates were similar as can be seen in Table 1:

Table 1. Outcomes after midurethral sling surgery in the obese population

Author	Year	Follow-up Mo	Procedure	BMI	No. of Patients	Cure Rate	
						Subjective	Objective
Mukherjee[38]	2001	6	TVT	<25	58	85%	
				25-29	98	95%	
				>30	87	89%	
Rafii[39]	2003	(27)	TVT	20-25	86	74%	93%
				26-30	62	72%	89%
				>30	39	72%	82%
Skriapas[40]	2006	(18)	TVT	<30	52	92%	90%
				>40	31	87%	90%
Ku[41]	2006	(10)	TVT	18.5-23	81	93%	
				23-27.5	159	91%	
				>27.5	45	84%	
Hellberg[36]	2007	(68)	TVT	19-24	291	81%	
				>35	61	52%*	
Killingsworth[42]	2009	12	TVT	<25	68	81%	
				25-29.9	65	86%	
				≥30	62	82%	
Rechberger[43]	2010	18	TVT	<25	41	81%	
				25-29.9	80	80%	
				>30	80	68%	
				<25	43	86%	
			TOT	25-29.9	81	72%	
				>30	73	70%	
Stav[44]	2010	(50)	TVT	<25	371	94%	
			TOT	>25	741	80%*	
Esin[45]	2011	12	TOT	<25	42	96%	92%
				>30	46	91%	91%
Haverkorn[46]	2011	(23)	TOT	<30	161	92%	
				>30	117	81%*	
Mohamad Al-Ali[47]	2011	12	TVT	<25	25	60%	76%
				25-30	33	61%	76%
				>30	35	49%	40%
Hwang[48]	2012	12	TVT	<22.9	90	94%	94%
				23-27.5	153	96%	97%
				>27.6	31	97%	97%
			TOT	<22.9	13	92%	100%
				23-27.5	33	94%	91%
				>27.6	3	67%	67%
Heinonen[49]	2013	(66)	TOT	<30	100	85%	
				>30	34	84%	

While Plaintiffs' experts opine that there is an increased risk of infection with the TVT and TVT-O mesh slings, the data do not bear this out. Overall, the risk of infection with the TVT and TVT-O mesh is very low. The Ford 2015 Cochrane Review analyzed data from several registries (Collinet 2008; Dyrkorn 2010; Kuuva 2002; Koops 2005; Tamussino 2001; Tamussino 2007; Tincello 2011) involving thousands of patients and found the infection rate for retropubic slings was 0.7% and for transobturator it was 0.6%. (Ford AA, Rogerson L, Cody JD, Ogah J. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. PMID: 26130017).

Infections and wound complications can and do occur with any SUI surgery. The Schimpf 2014 SGS systematic review and meta-analysis reported the following wound infection rates which show that TVT and TVT-O have lower rates than the pubovaginal sling and Burch:

- Obturator 0.74%
- Retropubic 0.75%
- Pubovaginal 2.6%
- Burch 7.0%

Similarly, in the SISTEr and TOMUS trials, both of which were conducted by the UITN, the authors reported wound complication rates as follows for both trials at 2 years:

Study	**UTIs**	**Wound Complications Requiring Surgery**	**Wound Complications Not Requiring Surgery**
Burch (*Albo 2007; n=329; 2 years*)	32% (n=105 with 203 events)	13 events	69 events
Fascial Sling (*Albo 2007; n=326; 2 years*)	48% (n=157 with 305 events)	11 events	71 events
TVT (*Albo 2012; n=298; 2 years*)	17.4% (n=52 with 64 events)	11 events	6 events
TVT-O/TOT (*Albo 2012; n=299; 2 years (TVT-O=161 & TOT=137*))	10.7% (n=32 with 35 events)	11 events	2 events

While mesh exposures were the most common wound complication in the TVT and TVT-O groups, other various wound complications occurred in the Burch and fascial sling groups:

- Wound complications requiring surgical intervention included incisional hernia (Burch, 5 patients; sling, 3), seroma or hematoma (Burch, 2; sling, 3), infection (Burch, 2; sling, 2), abscess (Burch, 1; sling, 1), and vaginal wound revision (Burch, 3; sling, 2).
- Wound complications not requiring surgical intervention included 2 sling exposures (visualization of the sling material in the vagina), incisional hernia (Burch group, 2; sling group, 1), superficial wound-edge separation (Burch, 10; sling, 5), seroma or hematoma (Burch, 13; sling, 11), infection (Burch, 31; sling, 21), and granulation tissue or stitch granulomas (Burch, 13; sling, 31).

Overall the data show that the rates of mesh exposure with TVT and TVT-O are in the 1 - 2.5% range and are manageable (Ford 2015 Cochrane Review: Retropubic 2.1% (21/1000), transobturator 2.4% (24/1000); Meta-analysis of Registries (Collinet 2008; Dyrkorn 2010; Kuuva 2002; Koops 2005; Tamussino 2001; Tamussino 2007; Tincello 2011): Retropubic 1.5%, transobturator 0.4%; Schimpf SGS 2014 Systematic review: Retropubic 1.4%, transobturator 2.2%; Novara 2008 Table 6 metaanalysis of 34 studies with >24 months follow up: TVT 1.1%.)

Studies on TVT and TVT-O also consistently report that there is a low rate of revision for voiding dysfunction, mesh exposure and other complications. As noted earlier, the metaanalysis by Novara of more than 30 TVT studies with more than 24 months follow up reported a 3.2% reoperation rate. The Ford 2015 Cochrane Review's assessment of multiple registries (n= 809 to 4281) found reoperation rates relating to

tape insertion or postoperative voiding dysfunction (POVD) from 1.6% to 2.4% for retropubic tape and 0.8% to 2.2% for transobturator tape. The Schimpf 2014 SGS systematic review and metaanalysis reported a 1.9% rate of return to the OR for erosion and 1.2% return to OR for urinary retention for retropubic slings and 2.7% and 1.1% rates for transobturator tapes.

Welk's recent analysis of Canadian databases involving 59,887 patients undergoing a SUI mesh sling reported a cumulative incidence rate for mesh revision/removal of 3.3% at 10 years follow up. (Welk B, et al. Removal or Revision of Vaginal Mesh Used for the Treatment of Stress Urinary Incontinence. JAMA Surg. 2015: 9:1-9.) These results are consistent with an analysis of data from US health maintenance organizations involving 188,454 eligible women who underwent an index sling that reported a 9-year rate of sling revision/removal of 3.7% consisting of 2.5% for mesh erosion and 1.3% for urinary retention. (Jonsson Funk M, et al. Sling revision/removal for mesh erosion and urinary retention: long-term risk and predictors. Am J Obstet Gynecol. 2013; 208:73.e1-7.).

A paper by Nguyen evaluating Kaiser Permanente data reported 2.2% of MUS patients had surgery consisting of 1.3% for voiding dysfunction or urinary retention, 0.8% for vaginal mesh erosion, 0.08% for urethral erosion, and 0.04% for pain (1/3,747). (Nguyen JN, et al. Perioperative complications and reoperations after incontinence and prolapse surgeries using prosthetic implants. Obstet Gynecol. 2012; 119:539-46.) A paper by Unger reported a 2.7% rate of reoperation (89/3,307) for slings, with revision

more common for voiding symptoms and/or urinary retention than mesh exposure. (Unger CA, et al. Indications and risk factors for midurethral sling revision. Int Urogynecol J. 2015 Jul 2 (e pub)). Like Nguyen's paper, reoperation due to vaginal pain/dyspareunia in Unger's paper was very rare overall in patients who received a sling, 7 of 3,307 patients (0.2%). Reoperation due to groin pain was a reason in 3.4% (n=3) of the 89 surgeries, which translates into a very rare overall absolute risk of 0.09% (3/3,307) of patients who received a sling.

In Laurikainen's five year RCT of TVT (n=131) versus TVT-O (n=123) noted above, complication rates were low, with no difference between groups, and none of the patients had any sign of tissue reaction, erosion, or tape protrusion at their 5-yr follow-up that included 95% assessment of enrolled patients. (Laurikainen E, et al. Five-year results of a randomized trial comparing retropubic and transobturator midurethral slings for stress incontinence. Eur Urol. 2014; 65:1109-14.) With regard to efficacy, the objective cure rate was 84.7% in the TVT group and 86.2% in the TVT-O group, subjective treatment satisfaction was 94.2% in the TVT group and 91.7% in the TVT-O group, and significant improvement was seen in all condition-specific QoL questionnaires for both groups, with no statistically significant differences between the groups.

In a 7 1/2 year study of 124 women undergoing TVT-O, objective and subjective cure rates were 81.5 % and 83.5 % with significant improvement in all KHQ domains. (Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator

(TVT-O) vaginal tape: why do tapes fail? Int Urogynecol J. 2014; 25:219-25.) There were no major perioperative complications. Reoperation for tape failure was low and occurred in three patients (2.4%). Only one patient (0.8 %) required tape division 3 months after surgery for voiding difficulties and one patient (0.8 %) had a midline mesh exposure diagnosed 1 year after the procedure that was excised. At the long term follow-up visit, no cases of vaginal erosions were detected and no patient reported persistent groin pain.

In the 5 year study by Serati, subjective and objective cure rates after TVT-O were 90.3% and 90.8%, and there were no long term mesh erosions or groin pain. (Serati M, et al. TVT-O for the treatment of pure urodynamic stress incontinence: efficacy, adverse effects, and prognostic factors at 5-year follow-up. Eur Urol. 2013; 63:872-8.) Eleven (5.8%) women reported early postoperative voiding dysfunction, but only in one case (0.5%) was TVT-O revision necessary. Vaginal erosion was recorded 12 months after TVT-O in two cases (1%) and one of these required sling removal (0.5%).

Tommaselli's recent systematic review and metaanalysis of 49 medium and long term studies showed that TVT-O was associated with a significantly lower incidence of vaginal injuries than TOT and there was no difference in persistent pain, defined as all pain reported beyond the perioperative period (>7 days after procedure), between RP-MUS and TO-MUS (2.2 % vs. 1.9 %). Persistent or chronic pain (i.e. pain persisting beyond the perioperative period or reported at the last follow-up visit) was very rare and reported by 13 patients for RP-MUS (13/3,974 = 0.3%) and 30 patients for TOMUS

(30/2,432 = 1.2%). (Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015; 26:1253-68.) Notably TVT and TVT-O represented the vast amount of data as they were represented in 43 of the 49 studies (Tables 1 and 2).

Overall, these data show that the TVT and TVT-O are very safe and effective based on high level studies with long follow up. The significant amount of level 1 evidence and long term data demonstrate that the TVT and the TVT-O and the macroporous Prolene polypropylene are optimal. Plaintiff's experts' claims that the mesh is cytotoxic, degrades, contracts, causes cancer and leads to an untoward inflammatory response are without support in the reliable scientific literature. The body of data on TVT and TVT-O do not demonstrate these concerns. While cytotoxicity was noted in an in vitro cell assay presented to the FDA in the 510k of TVT, the overall clinical data was also presented which did not show cytotoxicity. The clinical data since also do not demonstrate cytotoxicity or an adverse inflammatory effect, as the mesh incorporates, there is long term efficacy and low complications including wound complications as discussed earlier and below. Moreover, if the mesh was cytotoxic, it would not incorporate and there would be tissue necrosis in all of the patients implanted with TVT and TVT-O. This has not been demonstrated.

Degradation of the mesh has not been demonstrated by reliable data. While there have been reports of "surface cracking" such as that described in the Clave 2010

paper, the authors there confirm that the phenomenon which was only observable in a minority of specimens could not be demonstrated on analytical chemical testing. Moreover, the methodology of the paper was flawed and unable to rule out that the surface cracking was not biofilm. The data do not support that any surface cracking causes clinical symptoms. To the contrary, polypropylene is a stable and well-accepted biomaterial with a history of over five decades of use in mesh implants. While plaintiffs' experts hypothesize that surface changes lead to adverse clinical outcomes, this is not supported by the extensive peer-reviewed literature related to polypropylene mesh repairs and specifically to the TVT and TVT-O devices.

Prospective studies have followed patients with implanted with TVT and TVT-O for 5-17 years and show excellent durability and safety with the use of the macroporous Prolene polypropylene sling. (AUGS-SUFU FAQs by Providers on Mid-urethral Slings for SUI 2014; Tommaselli GA, et al. Medium-term and long-term outcomes following placement of midurethral slings for stress urinary incontinence: a systematic review and metaanalysis. Int Urogynecol J. 2015; 26:1253-68; Ford AA, et al. Mid-urethral sling operations for stress urinary incontinence in women. Cochrane Database Syst Rev. 2015 Jul 1;7:CD006375. [Epub ahead of print] PubMed PMID: 26130017; Nilsson CG, et al. Seventeen years' follow-up of the tension-free vaginal tape procedure for female stress urinary incontinence. Int Urogynecol J. 2013; 24:1265-69; Athanasiou S, et al. Seven years of objective and subjective outcomes of transobturator (TVT-O) vaginal tape: why do tapes fail? Int Urogynecol J. 2014; 25:219-25.)

Numerous data cited in my report show that the macroporous Prolene polypropylene tape is well tolerated and provides lasting efficacy for SUI. For example, in the 10 year study by Svenningsen which evaluated 483 women at a median duration of 129 months follow-up, there was a 90% objective cure rate, only 2.3 % of the women had undergone repeat SUI surgery, and the total number of exposures was 4 (0.8 %) for the whole 10-year period, with only 1 case of asymptomatic mesh exposure (0.2%) found at the 10-year follow-up. (Svenningsen R, et al. Long-term follow-up of the retropubic tension-free vaginal tape procedure. Int Urogynecol J. 2013; 24:1271-78.)

In the 10 year study by Serati, the 10 year subjective, objective, and urodynamic cure rates were 89.7%, 93.1%, and 91.4%, no patient required tape release or section during the 10 year follow-up, and there were no vaginal, bladder, or urethral erosion, or de novo dyspareunia noted. (Serati M, et al. Tension-free vaginal tape for the treatment of urodynamic stress incontinence: efficacy and adverse effects at 10-year follow-up. Eur Urol. 2012; 61:939-46). More recently, the 13 year study results by Serati were published and showed excellent efficacy and safety. (Serati M, et al. TVT for the treatment of urodynamic stress incontinence: Efficacy and adverse effects at 13-year follow-up. Neurourol Urodyn. 2015 Oct 19. doi: 10.1002/nau.22914. [Epub ahead of print]) The 13 year subjective, objective, and urodynamic cure rates were 85.5%, 90.9%, and 89.1%. Additionally, no patient required tape release or section during the 13 year follow-up, and there were no vaginal, bladder, or urethral erosion, or de novo dyspareunia noted.

In the 10.5 year study by Heinonen, objective and subjective cure rates were 90% and 78% and only three patients (2.3%) had adverse events at 1–11 years postoperatively. (Heinonen P, et al. Tension-free vaginal tape procedure without preoperative urodynamic examination: long-term outcome. Int J Urol. 2012; 19:1003-9.) Two patients with retention and pain had the tape cut without any further problems and the other patient had recurrent urinary tract infections and dysuria as a result of tape erosion into the bladder.

In the 10 year study by Aigmueller, only 2.8% of patients (4/141) had repeat incontinence surgery and there were 2 mesh related reoperations (1.4%) due to mesh erosion. (Aigmueller T, et al. Ten-year follow-up after the tension-free vaginal tape procedure. Am J Obstet Gynecol. 2011; 205:496.e1-5.) In the study by Olsson with a median 138 month follow up, there was only one case (0.8%, 1/124) of wound healing which occurred two months post-operatively, three cases of early tape release (2.4%) for retention, and there were no late adverse effect including erosion of tape rejection at long term follow up. (Olsson I, et al. Long-term efficacy of the tension-free vaginal tape procedure for the treatment of urinary incontinence: a retrospective follow-up 11.5 years post-operatively. Int Urogynecol J. 2010; 21:679-83). These data are inconsistent with Plaintiff's experts' theories.

There are no reliable scientific data that not show a risk of cancer and reliance by Plaintiff's experts on MSDS sheets and data in rats while attempting to extrapolate to humans is unreliable and improper methodology. (Moalli P, et al. Polypropylene mesh:

evidence for lack of carcinogenicity. Int Urogynecol J. 2014; 25:573-6; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014; 15:453.) There are no epidemiologic data which shows that there is a statistically significant risk compared to the background rate of malignancy. King reported a series of 2,361 polypropylene midurethral slings with a follow-up extending up to 122.3 months and the rate of cancer formation was 0.0 % and no sarcomas were reported. (King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology 2014; 84:789-92). As observed by AUGS and SUFU in their 2014 Frequently Asked Questions by Providers on MUS for SUI:

Tumors related to the implantation of surgical grade polypropylene for mid-urethral slings in humans have never been reported. There is no compelling evidence supporting human malignant transformation related to polypropylene despite the millions of individuals implanted with various forms of this material spanning well over a half century world-wide. The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of extensive research by both clinicians and biomaterial researchers. (McGregor, D.B., et al., Evaluation of the carcinogenic risks to humans associated with surgical implants and other foreign bodies - a report of an IARC Monographs Programme Meeting. International Agency for Research on Cancer. Eur J Cancer, 2000. 36(3): p. 307-13; Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.) It is known that tumor formation related to

biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being potentially carcinogenic, and irregular disrupted surfaces (e.g. those that contain pores as in meshes) lacking carcinogenicity (Ratner, B.D., et al., eds. Biomaterials Science: An Introduction to Materials in Medicine - 3rd Edition. 2013, Academic Press: Waltham, MA.; Oppenheimer, B.S., et al., The latent period in carcinogenesis by plastics in rats and its relation to the presarcomatous stage. Cancer, 1958. 11(1): p. 204-13.).

Most recently, a study of 2,474 patients who underwent polypropylene sling placement and followed for a median of 5 years demonstrated that there is no association between polypropylene and cancer or sarcoma in humans. (Linder 2016). Only 2 malignancies (0.08 %) occurred after sling placement while there 49 cancer diagnoses which preexisted the sling placement, demonstrating a much higher background rate of cancer. No cases were seen in patients with more than 10 years follow up. No data have shown a statistically significant higher rate of sarcoma formation or cancer compared to background rates in women.

Overall the data show that the TVT and TVT-O are safe and effective. The TVT was developed to provide for a less invasive, less morbid SUI surgery that could be performed in an ambulatory manner. The data show that it is highly effective in the long term and has less complications and in particular serious complications and voiding difficulties than the Burch colposuspension and autologous sling. The TVT-O followed in its design and it demonstrates high levels of efficacy along with an even lower rate of

serious complications. Like the TVT, the TVT-O is minimally invasive, less morbid and has less complications than the Burch colposuspension and autologous sling. Overall TVT and TVT-O lead to shorter operating times, shorter hospital stay, reduced operative pain, reduced voiding dysfunction, and a quicker recovery. TVT and TVT-O are the most studied devices for SUI surgery and they have been studied more than the Burch colposuspension and autologous sling. The macroporous Prolene polypropylene tape in TVT and TVT-O is the optimal material for SUI surgery. It is biocompatible and has demonstrated tolerability. Complications are low and manageable. While mesh exposure can occur, other wound complications occur in a significant portion of patients undergoing the Burch colposuspension and autologous sling. The design of both devices was and is state of the art and the vast majority of pelvic surgeons in the US and abroad prefer the polypropylene midurethral sling over the Burch colposuspension and autologous sling. TVT and TVT-O have been assessed in numerous high level data including RCTs, metaanalyses, systematic reviews and professional society guidelines, bulletins and position statements which rely on the highest levels of evidence. TVT and TVT-O have been found to be safe and effective in the short and long term, with low morbidity and complications, and having great utility and usefulness to surgeons and patients. Overall reoperation rates are low and complications are manageable.

Potential risks of SUI surgery are well described to surgeons during training, in medical textbooks, and in the medical literature, and are well known elemental risks that surgeons would be aware of. The same is true for the tensioning of sutures as well as slings, whether made of synthetic or animal or native tissue, and the potential

complications such as voiding dysfunction. Pain, pelvic pain, and dyspareunia can occur with any SUI surgery and vaginal surgery, are well known and described in the literature, as well as taught to surgeons in their education and training. Dyspareunia and sexual dysfunction that preexists in women can also be cured or improve following TVT or TVT-O placement. Mesh exposure/erosion is the only unique risk when using the TVT and TVT-O and it is uncommon and can be easily treated in the majority of cases. Suture and sling erosion and wound complications can occur with non-TVT/TVT-O SUI surgeries. These risks would be known by surgeons of the type to perform SUI surgery and would be obvious based on basic SUI surgical principles and knowledge as well as observation of the surgical instruments involved. The TVT and TVT-O are not defective in their design and from my perspective as a surgeon, the risks are adequately described in the IFU and professional education materials, and would be known by pelvic surgeons and obvious.

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